I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

On December 22, 2005

TOWNSEND and TOWNSEND and CREW LLP

By: Karen Karlin

PATENT
Attorney Docket No.: 018512-006610US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Wickenden et al.

Application No.: 09/939,230

Filed: August 24, 2001

For: METHODS FOR TREATING OR PREVENTING PAIN AND ANXIETY

Customer No.: 20350

Examiner: Jones, Dwayne C.

Technology Center/Art Unit: 1614

DECLARATION OF DR. DOUGLAS S. KRAFTE UNDER 37 CFR § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, Douglas S. Krafte, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

2. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

3. I am currently employed by Icagen Inc. as a Vice President of Biology. I received a Ph.D. in 1986 in Physiology from the University of Rochester. I received a B. Sc. in 1981 in Molecular Biology from Vanderbilt University. I have conducted research in the field of pharmaceutical drug discovery for approximately 16 years.

4. I am familiar with the subject matter contained in the above-referenced patent application, "METHODS FOR TREATING OR PREVENTING PAIN AND ANXIETY."

5. I have read and I understand the Office Action mailed by the Examiner on June 28, 2005.

6. I have read and I understand the currently pending claims, including amended claim 45.

7. I understand that claims 45-67 and 70-82 stand rejected under 35 U.S.C. § 112, as allegedly non-enabled. I understand from counsel that the test for enablement is whether one skilled in the art could make or use the claimed invention from the disclosure in the patent application coupled with information known in the art without undue experimentation. I also understand from counsel that routine screening of even large numbers of samples does not constitute undue experimentation for purposes of determining enablement.

8. A large number of KCNQ channel openers are disclosed both explicitly and implicitly in the specification. In addition to the KCNQ channel openers explicitly set forth in Figure 7, the specification also discloses the many structurally diverse KCNQ channel openers set forth in USSN 60/158,712, filed October 8, 1999, from which the current application claims priority. USSN 60/158,712 discloses a variety of N-aryl, N-alkyl, and N-cycloalkyl pyrazole amide KCNQ channel openers. The present specification also sets forth a number of compounds in the form of chemical genuses and subgenuses. It my scientific opinion that any or all of these compounds may be routinely tested for their ability to reduce anxiety in a subject using assays widely known in the art at the time of filing this application, as well as assays explicitly disclosed in this application.

9. A number of simple assays to identify KCNQ channel openers are explicitly set forth in the specification. The assays involve the *in vivo* or *in vitro* contacting of a sample having a KCNQ channel with a test compound followed by measurement of the KCNQ potassium channel activity. See specification, page 23, lines 25-29. The activity of the test compound may then be compared with untreated control samples. See specification, page 23, lines 27-29. These assays can be conducted using high throughput screening methods and large libraries of chemical compounds, which are well known in the art. Systematic screening of potential KCNQ channel openers can be aided by robotic automation. See specification, page 25, lines 21-27. KCNQ potassium channel opening activity may be determined by measuring changes in ion flux through detection of cell or membrane polarization. See specification, page 24, lines 4-6. Cell or membrane polarization is detected by measuring changes in current using standard techniques such as voltage clamps or patch clamps. See specification, page 24, lines 6-10. These assays can be used routinely to determine whether or not a selected compound acts as a KCNQ channel opener.

10. The specification further discloses other routine assays for measuring ion flux, including those involving the measurement of potassium or rubidium ions flux by directly detecting the concentration changes of the ions (e.g., radioisotopic labeling). See specification, page 24, lines 23-32. In addition, ion flux may be measured by determining changes in physiological conditions, such as transmitter release (e.g., dopamine), hormone release (e.g., insulin), transcriptional changes to both known and uncharacterized genetic markers (e.g., northern blots), cell volume changes (e.g., in red blood cells), immunoresponses (e.g., T cell activation), changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as Ca^{2+}, or cyclic nucleotides. See specification, page 24, line 30 to page 25, line 8.

11. The specification further provides additional routine methods useful in identifying KCNQ channel openers, such as measuring current; measuring membrane potential; measuring ion flux; e.g., potassium or rubidium; measuring potassium concentration; measuring second messengers and transcription levels, using potassium-dependent yeast growth assays; measuring pain responses in mice, e.g., with formalin algesia or hotplate assays; measuring

ligand binding; and using, e.g., voltage-sensitive dyes, radioactive tracers, and patch-clamp electrophysiology. See specification, page 23, lines 12-18.

12. The specification also sets forth simple and routine assays to test potassium channel openers for their ability of treat anxiety, such as the standard Geller conflict procedure.

13. The above assays were well known in the art at the time of filing the application, as evidenced by the references cited therein (Ackerman *et al., New Engl. J. Med.* 336:1575-1595 (1997); Hamil *et al., Pflugers. Archiv.* 391:85 (1981); Vestergarrd-Bogind *et al., J. Membrane Biol.* 88:67-75 (1988); Daniel *et al., J. Pharmacol. Meth.* 25:185-193 (1991); Holevinsky *et al., J. Membrane Biology* 137:59-70 (1994); Blatz *et al., Nature* 323:718-720 (1986); and Park, *J. Physiol.* 481:555-570 (1994)).

14. It is well within the capabilities of those skilled in the art to routinely test compounds for their ability to open KCNQ channels and to treat anxiety (e.g. using the Geller conflict procedure). I am not aware of any reasons as to why one skilled in the art would doubt the usefulness of the routine assays disclosed in the specification that I have identified in paragraphs 19-13 above.

15. Therefore, it is my scientific opinion that one skilled in the art, using the teachings in the specification and methods generally known in the art, would be able to determine the ability of the KCNQ channel openers recited in amended claim 45 to treat anxiety in a subject.

16. The specification provides a working example of the claimed invention in which a KCNQ channel opener is administered in accordance with the protocol of the Geller conflict model. See Example 6. It is my scientific opinion that this example demonstrates that the invention as recited in claim 45 works for its intended purpose. I am aware of no evidence or reasoning as to why one skilled in the art would doubt the validity of this experiment.

17. In view of the above, it is, therefore, my scientific opinion, that one skilled in the art would recognize that Applicants enabled a method of reducing anxiety using a compound that increases ion flow through a KCNQ potassium channel as set forth in claim 45.

Dated: 12/20/2005

Douglas S. Krafte

60657440 v1